REMARKS

1. Introductory remarks

Claims 1, 3, 4, 6, 15, 16, 18, 19, 21, 22 and 24 were pending before the Office. By this Amendment, Applicants respectfully request that claim 1 be amended and claims 3, 15, 16, 18, 19, 21, 22 and 24 be cancelled, without prejudice. No claims are added. Thus, claims 1, 4, and 6 shall remain pending after entry of this Amendment.

The amendments have been made solely to clarify the invention and/or to expedite prosecution of the present application and should in no way be construed as an acquiescence to any of the Examiner's rejections in the Office action issued in the present application. Applicants reserve the right to pursue the subject matter of the claims as originally filed or similar claims in one or more subsequent applications.

No new matter has been added by these amendments as support for the amendments can be found throughout application, including the specification, drawings, examples and claims, as originally filed.

Accordingly, no new matter has been added by this amendment.

Reconsideration and withdrawal of the rejections of this application in view of the amendments and remarks herewith, are respectfully requested.

2. The Rejection Under 35 U.S.C. 102(e) Is Overcome

The Office Action maintains the rejection of claims 1, 4, 6, 15, 18 and 19 under 35 U.S.C. 102(e) as allegedly being anticipated by Eveleigh et al. (US 2004/0121375). More in particular, the Office Action contends that:

> *Eveleigh et al disclose a method comprising (a) determining the level of expression of one or more biomarker(s) in a first biological sample taken from the patient prior to treatment with the anti-cancer agent; (b) determining the level of expression of the biomarker in at least a second biological sample taken from the patient subsequent to the initial treatment with the anti-cancer agent...Eveleigh et al. disclose that the biomarkers are detected by immunohistochemical analysis [0120] and that the anti-cancer agent is a raf kinase inhibitor.*

As an initial matter, the rejection of claims 15, 18 and 19 is moot as those claims are now cancelled. As to the remaining claims under rejection, Applicants disagree with the rejection and respectfully traverse as follows.

The Examiner is respectfully pointed to M.P.E.P § 2131 which states that "[a] claim is anticipated ***only if each and every element*** as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987) (emphasis added). It will be shown below that Eveleigh does not expressly or inherently teach each and every element of the claimed invention, and thus, does not anticipate the present claims.

The present invention, as reflected in independent claim 1, is directed to a method to monitor the response of a patient being treated for cancer to the administration of a small molecule Raf kinase inhibitor. This method includes determining the *phosphorylation level* of pERK in a first biological sample taken from the patient prior to treatment with the small molecule Raf kinase inhibitor *and* determining the *phosphorylation level of pERK* in at least a second biological sample taken from the patient subsequent to the treatment with the small molecule Raf kinase inhibitor. The method then compares the phosphorylation level in the second biological sample with the phosphorylation level in the first biological sample, thereby indicating a response of the patient being treated for cancer to the administration of the small molecule Raf kinase inhibitor.

Eveleigh et al. does not teach or fairly suggest the present invention as presently claimed. More in particular, Eveleigh et al. relates to the use of adrenomedullin—not pERK or the *phosphorylation level* of pERK—as a biomarker for evaluating Raf kinase inhibitors through the use of gene expression profiling and other related molecular tests. Eveleigh is focused on the "link between adrenomedullin and Raf kinase" (see paragraph 007 of Eveleigh et al.) and does not pertain to or disclose any connection between Raf kinase inactivation and pERK or the *phosphorylation level* of pERK, in the manner prescribed by the instant claims.

Eveleigh et al. also does not teach or suggest a method to monitor the response of a patient being treated for cancer to the administration of a small molecule Raf kinase inhibitor. Nor does Eveleigh et al. contemplate a method for identifying whether a candidate *small molecule Raf kinase inhibitor* is effective for the treatment of cancer based on the effects of the candidate inhibitor on the *phosphorylation level* of pERK. Eveleigh et al. simply does not recognize or contemplate any connection among an inhibitor of Raf kinase, the level of

phosphorylation of pERK, and the responsiveness or sensitivity of a cancer patient to the Raf kinase inhibitor drug. The use or recognition of pERK as a biomarker is simply not contemplated by Eveleigh et al.

Accordingly, Eveleigh et al. does not teach or suggest all of the elements of the instantly claimed invention and thus, does not anticipate claim 1. In addition, since all of the remaining claims ultimately depend from claim 1, and thus, incorporate all of the limitations of claim 1 therein, Eveleigh et al. also does not anticipate the remaining rejected claims. Applicants respectfully request reconsideration and withdrawal of the Section 102 rejection.

Applicants would like to additionally note that Eveleigh et al. also would not qualify as prior art under Section 103 as it is would benefit from the exclusion under 35 U.S.C. 103(c). Eveleigh and the instant patent application were each separately assigned to Bayer Pharmaceuticals Corporation. The assignment of Eveleigh et al. is recorded at Reel/Frame 014375/0623. The assignment of the present invention (against the published application, US 2007/0292887) is recorded at Reel/Frame 017469/0854. The inventors of both Eveleigh et al. and of the present invention would have been obligated to assign their right, title and interest in their respective inventions to Bayer Pharmaceuticals Corporation at the time of the present invention given the requirements of their employment contracts with the company. Because the conditions of Section 103(c) can be met, the present invention cannot be rendered obvious over Eveleigh et al.

3. The Rejection Under 35 U.S.C. 103 Are Overcome

The Office Action rejects claims 1, 3, 4, 6, 15, 16, 21, 22 and 24 under 35 U.S.C. 103(a) as allegedly being unpatentable over Bacus et al. (US 2003/0045451) in view of Mantlo et al. (US 6,174,901) and Sivaraman et al. (US 6,007,991).

Particularly, the Office Action states that Bacus et al. "teaches a method comprising obtaining a first tissue or cell sample from an individual prior to exposure to a therapeutic agent; obtaining a second tissue or cell sample from said individual after exposure to a therapeutic agent, and comparing the amount or one or a plurality of biological markers in said first and second tissue sample." However, the Action admits that "Bacus does not specifically teach tyrosine kinases inhibitors that inhibit Raf kinase." As to Mantlo et al., the Office Action states

that the reference teaches that Raf kinase antagonists can be useful in the treatment of cancer and that "Raf kinase activity can be measured in vitro by the extent of substrate phosphorylation, wherein the substrate is Map kinase/ERK." Sivaraman et al. appears to be cited for its purported teaching that the level of ERK can be determined by immunohistochemical staining.

Based on these characterizations of the references, the Office concludes that "it would have been *prima facie* obvious at the time that the claimed invention was made to substitute the screening of Raf kinase inhibitors [of Mantlo et al.] for the screening of c-kit inhibitors in the method of Bacus. It would also have been obvious to use phosphorylated ERK as a marker for modulation of Raf kinase by using immunohistochemically detecting phosphorylated ERK." Applicants respectfully disagree with the rejection and traverse as follows.

As an initial note, the rejection is moot as to claims 15, 16, 21, 22 and 24 because those claims have been cancelled. As to the remaining claims under rejection, Applicants respectfully submit the following.

As the Office will appreciate, *Graham v. John Deere Co.,* 338 U.S. 1, 148 USPQ 459 (1966), was reaffirmed by *KSR International Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) as providing the correct analytical framework for determining obviousness. Under *Graham*, obviousness is a question of law based on underlying factual inquires that address (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, and (3) the level of ordinary skill in the pertinent art. Additionally, the Supreme Court in *KSR* required a "clear articulation of the reason(s) why the claimed invention would have been obvious" and that such reason "supporting a rejection under 35 U.S.C. 103 should be made explicit."

Here, the Office Action argues for each rejection that the combination of references is proper because there exists some teaching, suggestion, or motivation in the prior art that would have led the skilled artisan to modify or combine the cited references to arrive at the claimed invention. In particular, the Office contends that "one of skill in the art would have been motivated to do so by the teachings of Mantlo et al. on antagonists of Raf kinase in the treatment of cancer, and the assay of Raf kinase activity by assaying ERK phosphorylation." However, as

discussed below, this appears to be a mischaracterization of Mantlo et al. because Mantlo et al. teaches the assaying of MEK, not ERK or ERK phosphorylation.

For the obviousness rejection to be proper, the prior art references or their combinations must be shown to ***teach or suggest all the claim limitations***. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). In addition, the rationale set forth by the Office is only proper to support the rejection where there is a clear (1) a ***teaching, suggestion or motivation to combine*** the references and (2) ***a finding of a reasonable expectation of success***. Accordingly, prior art combinations which teach or suggest all the claim limitations may be modified or combined to reject claims as *prima facie* obvious under the Office's rationale as long as there is a reasonable expectation of success and a reason to combine. Such is not the case here.

Applicants respectfully submit that the obviousness rejections cannot stand because the references in combination do not teach or fairly suggest all of the claim limitations. Moreover, it is believed that the Office has mischaracterized Mantlo et al. as teaching the measuring of ERK phosphorylation as a gauge of Raf kinase activity, when it clearly does not provide such a teaching. Moreover, even if, *arguendo*, the references were inclusive (expressly or by suggestion) as to all of the claim limitations (which is not the case), no motivation to combine the references would have existed at the time of the invention because the references teach away from their own combination and/or at least show that one of ordinary skill in the art would have lacked a reasonable expectation of success that the alleged combination would have reached the instantly claimed invention. Thus, the obviousness rejections should be reconsidered and withdrawn.

As noted, none of the references of Bacus et al., Mantlo et al., or Sivaraman et al.—either considered alone or in any combination—teach or fairly suggest all of the claim limitations of the present invention. The present invention provides a method which can be used to monitor cancer patient responses to *small molecule* Raf kinase inhibitors or screen for such *small molecule* compounds by essentially *comparing the phosphorylation level of pERK* before and after exposure or administration of a small molecule Raf kinase inhibitor (or candidate thereof), wherein a difference in the *pERK phosphorylation level* is indicative of an effective Raf kinase

inhibitor. Bacus et al, Mantlo et al. and Sivaraman et al., either alone or when combined, do not teach or suggest these features.

Bacus et al. relates to methods for detecting the expression and/or activation of proteins and ligands that are involved in the activation of the tumor-related signal transduction protein, AKT, or inducing the expression of the gene encoding AKT [an angiogenesis-inhibiting product]. The Bacus et al. specification states that the "invention specifically provides methods for quantitatively determining expression and activation levels for cellular proteins encoded by c-kit, SCF and AKT, in tumor cells, including human tumor cells, as detected in cell or tissue sample from an individual." In addition, the reference proposes monitoring the expression and/or activation levels of the tumor markers c-kit, SCF and AKT in connection with the administration of inhibitors of same as a measure of the utility of such compounds against those tumor markers.

Bacus et al. does not teach or suggest or even contemplate the use of ERK or the phosphorylation level of ERK as a marker for Raf kinase activity. Instead, Bacus et al. relates to a set of very distinct biological tumor markers (c-kit, SCF, pc-kit and AKT) and does not at any point discuss or suggest the testing or screening or administering a Raf kinase *in vitro* or *in vivo* to an actual patient, as is required by the present invention.

At one point, as noted in the Action, Bacus et al. mentions (paragraph 0085) that a series of other "tumor-related genes" (including pERK) can also be "detected and quantitated" in connection with the effects on their expression of the main tumor-markers of the specification of c-kit, SCF, pc-kit and AKT. However, this mentioning of ERK has nothing to do with the present invention because Bacus et al. does not teach to measure the *level of phosphorylation of pERK as a marker for the effectiveness of a Raf kinase inhibitor*. Like Eveleigh et al., Bacus et al. simply does not contemplate a method for identifying whether a candidate *small molecule Raf kinase inhibitor* is effective for the treatment of cancer based on the effects of the candidate inhibitor on the *phosphorylation level* of pERK.

Mantlo et al. does not make up for the deficiencies of Bacus et al. nor can it be relied on by itself as a teaching or suggestion of the present invention. Mantlo et al. teaches a class of substituted pyridines and pyridazine compounds that are suggested to be useful in the treatment

of a variety of diseases mediated by TNF-α, IL-1-β, IL-6 and IL-8 or conditions involving inflammation. The compounds were characterized *in vitro* as to their capacities to inhibit TNF-α and IL-1-β, inhibit glucagon binding, inhibit COX-1 and COX-2, and inhibit Raf-kinase. However, and importantly, Mantlo et al.'s Raf-kinase inhibition assay was *in vitro* and involved determining the amount of inhibition of *MEK* phosphorylation. While the *MEK* protein is part of the Raf/Mek/Erk signal transduction pathway, MEK is not the same protein as ERK and occurs at an earlier point in the mitogenic kinase cascade defining the pathway. Thus, ***none of Mantlo et al.'s disclosures teach or suggest the present invention.***

The present invention involves an actual cancer patient who is undergoing a treatment using a Raf kinase inhibitor. Mantlo et al. does not teach or suggest this aspect of the invention. Instead, Mantlo et al. teaches various ways to characterize its compounds using various *in vitro assays* (see columns 74-75), none of which contemplate determining the effectiveness of a Raf kinase inhibitor with the *level of phosphorylation of pERK,* as claimed.

Sivaraman et al. does not make up for the deficiencies of either Mantlo et al. or Bacus et al., nor does it by itself render the present invention obvious. Unlike the present invention, Silvaraman et al. is concerned with methods of targeting ERK-1 or ERK-2 with *oligonucleotide* compositions as a means to inhibit their *level of expression*. Indeed, Sivaraman et al. teaches the its "method includes the steps of (a) determining the level of expression of ERK-1, ERK-2, or both in epithelial or endothelial cells suspected of malignant neoplastic growth…and ascertaining whether said level of expression determined in step (a) is higher than the level of expression of ERK-1." As these teaching relate to the *targeting* of ERK, rather than to the assessment of the phosphorylation state of ERK *in connection with or as a biomarker* as to the effectiveness of a Raf kinase inhibitor small molecule drug, Silvaraman et al. is far removed from the present invention and does not teach or suggest, either alone or in combination with the other references, the present invention.

Accordingly, none of the references of Bacus et al., Mantlo et al., or Sivaraman et al.—either considered alone or in any combination—teach or fairly suggest all of the claim limitations of the present invention.

Moreover, even if all of the limitations of the claims were taught or suggested by the above combination (which is not the case), one or ordinary skill in the art would have lacked the necessary motivation to make their combination, particularly in view of the "teachings away" from the invention in Sivaraman et al. In particular, Sivaraman et al. teaches that:

> *However, these strategies of inhibiting or inactivating the upstream regulators of MAP kinase, such as ras,* ***raf-1*** *and MEK,* ***have generally not been effective****. It is becoming apparent that the proliferation pathway blocked by the inhibition* ***may be replaced by other pathways*** *that promote unregulated cell proliferation. The replacement pathway may occur in the malignant cells treated with the antisense oligonucleotides, or in clones of other malignant cells that co-exist with the treated cells.*

One or ordinary skill in the art upon reading Sivaraman et al. would not be guided towards the present invention, either considered by itself or in combination with Bacus et al. or Mantlo et al. because the teachings suggest the high degree of complexity that exists with signal transduction pathways, including that unexpected compensatory pathways may come into play at a point downstream of the inhibited regulator (e.g., Raf kinase). Thus, while the kinase cascade involves Raf kinase, MEK and then ERK, the Sivaraman et al. reference suggests that by inhibiting Raf kinase, one should not necessarily expect a concomitant decrease in the phosphorylation level of either MEK or ERK—downstream points at which other compensatory replacement pathways may be involved in, for example, maintaining their levels of phosphorylation at some steady state.

Thus, given the complexity and uncertainty in signal transduction pathways recognized in the prior art, one of ordinary skill in the art would not have been motivated to combine any of the teachings of Mantlo et al. and Bacus et al. to reach the present invention because of the known unpredictability in signal transduction pathways and the recognized lack of effectiveness of Raf kinase inhibition as expressed in Sivaraman et al. Thus, not only does the combination of the references cited by the Office fail to teach or suggest the present invention, there would have been no motivation to assemble the combination in the first place because of Sivaraman's suggestion that the strategy of Raf kinase inhibition lacks effectiveness.

Moreover, given the assertion by Sivaraman that Raf kinase lacks effectiveness as a strategy, one of ordinary skill in the art also would have lacked a reasonable expectation of

success in carrying out the claimed invention on the basis of the asserted combination of references. The present invention is directed to monitoring cancer patient responses to the administration of small molecule Ras kinase inhibitors essentially by *comparing the phosphorylation level of pERK* before and after exposure or administration of the small molecule Raf kinase inhibitor, wherein a difference in the *pERK phosphorylation level* is indicative of an effective Raf kinase inhibitor. Sivaraman et al. teaches that strategies of inhibiting upstream regulators of MAP kinase, including Raf kinase inhibition, has traditionally lacked effectiveness. Thus, a skilled artisan would not have reasonably expected that the instant invention would have worked as claimed.

In view of at least the above, Applicants respectfully request reconsideration and withdrawal of the Section 103 rejection over Bacus et al., Mantlo et al. and Sivaraman et al. is respectfully requested.

4. The Obviousness-Type Double-Patenting Rejection Is Overcome

The Office Action provisionally rejects claims 1, 2, 4, 5, 15, 18 and 19 as being unpatentable over claims 1-3 and 6 of copending Application No. 11/589,295. Initially, the rejection is moot as to claims 5, 15, 18 and 19 because those claims are cancelled. As to the remaining claims, Applicants disagree with the rejection and traverse as follows.

None of the claims over which the instant claims are cited teach or suggest the notion of measuring the phosphorylation level of pERK in relation to the activity or effectiveness of a Raf kinase inhibitor. Instead, the copending claims are directed to a method for monitoring the response of a patient being treated for cancer by administering *sorafenib* ("Nexavar"). These claims do not involve the particular claimed steps of the invention, and thus, do not render the present claims obvious.

In addition, Applicants wish to point out that the instant application was filed before the cited copending application. Thus, according to M.P.E.P. 804(I)(B(1), the provisional nonstatutory obviousness-type double patenting rejection should be withdrawn to permit the issue of a patent, if no other grounds for rejection or objection exist and where the later-filed application is rejectable on other grounds, without requiring the Applicants to file a terminal disclaimer.

Nevertheless, it remains unknown what subject matter claimed and disclosed in the present application will be deemed allowable; hence any statement regarding this rejection made on Applicants' part would be premature. Therefore, Applicants respectfully traverse this rejection, but also request that this rejection be held in abeyance until subject matter is deemed allowable in this application. Applicants will consider filing a terminal disclaimer, if necessary, to overcome any remaining rejections at the time allowable subject matter is known.

CONCLUSION

In view of the remarks herein, Applicants respectfully request reconsideration and withdrawal of all of the rejections as Applicants believe the application to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105 under number 67859(303981).

Dated: February 9, 2010

Respectfully submitted,

By: /Gabriel J. McCool/

Gabriel J. McCool, Reg. No. 58,423
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(203) 975-7505